

APPENDIX A.

**CLINICAL VALIDATION OF THE AMERICAN FERTILITY
SOCIETY ADNEXAL ADHESION SCORING SYSTEM:
REVIEW OF THE LITERATURE**

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1.0 EXECUTIVE SUMMARY

Prevention or amelioration of surgical adhesions is an important goal for every surgeon and for every patient. There are few methods available for prevention of adhesions, resulting in a large unmet need; however, products currently available for reduction of surgical adhesion formation were approved on the basis of "surrogate endpoints" for measurement of effectiveness. That is, effectiveness for these products was demonstrated via measurement of adhesion incidence, severity, and extent, rather than using a clinical outcome.

The most widely used system available (and the current standard of practice) for scoring adhesions is the American Fertility Society Classification of Adnexal Adhesions, in use for over 10 years. In this document, clear evidence is presented of a direct correlation between adnexal adhesion score as measured by the Classification of the American Fertility Society and clinical outcome, as demonstrated in multiple clinical studies published in peer reviewed journals.

2.0 INTRODUCTION

Abdominal and pelvic fibrous adhesions are common sequelae of surgical procedures, infections such as pelvic inflammatory disease, and endometriosis (Mage et al. 2000, Operative Laparoscopy Study Group 1991). In particular, myomectomy is associated with high adhesion rates; more than 60% of patients are affected (DeCherney, unpublished). It is generally agreed by surgeons that the clinical impact of adhesions is considerable (Scott-Coombes et al. 1993). Adhesions are implicated as the most common cause of bowel obstruction, and contribute to such common problems as chronic pain and infertility (Caspi et al. 1979, Keltz et al. 1995, Mueller et al. 1995, Menzies 1993). Reformed adhesion rates can be as high as 90% (Adhesion Study Group 1983, DeCherney, unpublished). Formation of fibrous adhesions is a non-specific response to tissue injury, occurring within weeks to a few months after the initiating insult. At second-look laparoscopy, three types of postoperative adhesions are recognized: *de novo* adhesions at the sites of surgical incisions; *de novo* adhesions at sites other than the prior surgery (non-surgical *de novo* adhesions); or reformed adhesions at the site of previous adhesiolysis (Operative Laparoscopy Study Group 1991).

Approaches to minimizing the deleterious effects of adhesions include: (1) subsequent surgical correction by adhesiolysis; (2) minimizing tissue damage with good surgical technique; and (3) preventive measures such as instilled solutions or locally applied adhesion barriers (e.g., INTERCEED, Seprafilm). Intrauterine pregnancy rates after adhesiolysis generally range from 38% to 57% (Caspi et al. 1979, Diamond 1979, Frantzen and Scholsser 1982, Tulandi 1986), and was reported to be 81% in another review of the literature (Filippini et al. 1995). Adhesiolysis provides symptomatic pain relief in as many as 80% of patients (Chan and Wood 1985, Keltz et al. 1995, Mueller et al. 1995, Steege and Stout 1991).

Clinical outcomes such as change in chronic pain or fertility are multi-factorial, making it difficult to test the effects of adhesiolysis or adhesion prevention using these endpoints. For this reason, many experts believe that adhesion reduction by itself is a valid clinical endpoint, measured using surrogate endpoints such as second-look adhesion formation (testimonies by Dr. Alan DeCherney, Dr. Jim Burns, Dr. Russell Malinak, Dr. Steven Wexner, Dr. Harold Ellis, Dr. Nancy Sharts-Hopko, Dr. Gerald Shirk, Dr. Subir Roy, Dr. Michael Diamond, Obstetrics and Gynecology Devices Panel Meeting, FDA, January 25, 2000, Adhesion Study Group 1983). Given the clinical significance of adhesions, the development of products and procedures to prevent adhesion formation are of great current clinical interest (Bronson and Wallach 1977, Diamond 1998, Fayez and Schneider 1987, Mueller et al. 1995, Peters et al. 1992, Obstetrics and Gynecology Devices Panel Meeting, FDA, January 25, 2000).

Currently available products intended as adjuncts to reduce the incidence of surgical site adhesions include INTERCEED Absorbable Adhesion Barrier and Seprafilm Bioresorbable Membrane. The effectiveness of these products has been established using "surrogate endpoints," that is, via measurement of adhesion incidence, severity and extent rather than a clinical outcome such as pain, bowel obstruction or fertility. The present review provides a summary of the clinical literature on approaches to the assessment of surgical adhesions, and a critical examination of the data regarding the most widely used system – that developed by the American Fertility Society (AFS) for classification of adnexal adhesions – and fertility outcome.

3.0 ADHESION SCORING SYSTEMS

Adhesion scoring systems have been developed to help establish correlations with disease outcomes and guide in management. These correlations are most clearly established when adhesions are graded numerically rather than simply qualitatively. As recently described in a textbook chapter regarding adhesion classification systems (Mage et al. 2000), adhesion scoring is not only used for prognosis, but also can be a determinant of therapy. Many physicians decide between *in vitro* fertilization and surgical approaches for infertility such as salpingostomy, based on adhesion scores. However, these authors point out that numerous adhesion classification systems are in use (20 independent systems were identified in 1995), often making it difficult to compare published clinical studies and impossible to identify an extensive literature using any specific system. The most widely used system is the American Fertility Society (AFS) Classification of Adnexal Adhesions (American Fertility Society 1988).

3.1 AMERICAN FERTILITY SOCIETY (AFS) CLASSIFICATION OF ADNEXAL ADHESIONS

In 1988, the AFS published the classification scheme for adnexal adhesions which is referred to here as the AFS score. This system is limited to the ovaries and tubes, and each adnexum is scored separately. Prognosis is based on the adnexa with the lesser amount of pathology. Scores are assigned on the basis of the type (filmy or dense) and extensiveness of the adhesions as shown in Table 3.1 below. Dense adhesions

are given a score 4 times greater than that of filmy adhesions. The scores assigned if the adhesion encloses 1/3 of the organ are doubled when the enclosure is between 1/3 to 2/3 and quadrupled when the enclosure is greater than 2/3. Thus, the score for each ovary or each tube could range from 0 to 16 (0, 1, 2, 4, 8, or 16), and for each adnexa the score could range from 0 to 32. After summing up the total scores, the degree of adhesions is classified as minimal (0 to 5), mild (6 to 10), moderate (11 to 20) and severe (21 to 32).

Table 3.1
THE AMERICAN FERTILITY SOCIETY CLASSIFICATION OF ADNEXAL ADHESIONS

	Adhesion Severity	Extent		
		<1/3 Enclosure	1/3-2/3 Enclosure	>2/3 Enclosure
RIGHT OVARY	Filmy	1	2	4
	Dense	4	8	16
RIGHT TUBE	Filmy	1	2	4
	Dense	4	8	16
LEFT OVARY	Filmy	1	2	4
	Dense	4	8	16
LEFT TUBE	Filmy	1	2	4
	Dense	4	8	16

Reference: American Fertility Society 1988

The AFS Classification of Adnexal Adhesions, with its consideration of types and extents of adhesions, has been well supported by clinicians both in published scientific literature (see below) and in presentations before the Food and Drug Administration (FDA) (Roy, unpublished; Diamond, unpublished; Adhesion Study Group 1983).

4.0 REVIEW OF THE LITERATURE: CORRELATION OF THE AMERICAN FERTILITY SOCIETY ADHESION SCORING SYSTEM AND CLINICAL ENDPOINTS

A literature search was performed to identify peer-reviewed published clinical literature in which the American Fertility Society adhesion scoring system was used in a patient population, and a correlation was made with relevant clinical outcomes. Following is a description of the methodology used to search the literature, and a review of the currently available literature correlating adhesion formation and the clinical outcomes of fertility and pregnancy.

4.1 METHODOLOGY OF LITERATURE ASSESSMENT

The adhesion classification system proposed by the American Fertility Society (1988) has been extensively adopted and is the most commonly used method for quantifying adhesions (Mage et al. 2000). To evaluate the clinical utility of the American Fertility Society Classification of Adnexal Adhesions, a search was performed of the English literature presenting correlating adhesion scoring with clinical outcomes. Search criteria included the terms "pelvic, adhesions, scoring, American Fertility

Society," and references within publications were "tree-searched" for additional citations. The databases searched were MEDLINE (1966-2000), Toxline (1965-2000), Biosis Reviews (1969-2000), EMBASE (1974-2000), and SciSearch (1990-2000).

4.2 RESULTS

Twenty-seven publications were identified that correlated adhesion score with clinical outcome. Of these, seven utilized the adhesion classification system of the American Fertility Society in a total of 732 patients and correlated adhesion scoring to fertility outcome measures (see Table 4.1). In the remaining 20 papers, investigators used either less detailed classifications of adhesions (*e.g.*, descriptions of either adhesion physical characteristics or extent, but not both), or the investigator used classification systems that included many additional sites besides the ovary and fallopian tube. No other classification system other than the American Fertility Society Classification of Adnexal Adhesions was used by more than a single set of investigators.

In 24 other papers identified with adhesion scoring data, investigators typically used either the American Fertility Society Classification of Adnexal Adhesions or a modification of the method that similarly assessed adhesion type and extensiveness. Adhesion scores were used as part of their patient characterization in these studies, but investigators did not provide any relevant clinical outcome data.

Table 4.1
LITERATURE THAT CORRELATED THE AMERICAN FERTILITY SOCIETY
CLASSIFICATION OF ADNEXAL ADHESIONS SCORE WITH
FERTILITY

CITATION	PURPOSE OF STUDY	RESULTS	CONCLUSIONS
De Bruyne et al. 1997	Correlate salpingostomy with AFS adhesion scoring system and pregnancy outcome	Non-significant trend for pregnancy rates compared between minimal-mild and moderate-severe adhesions ($p=0.051$)	Trend suggests that the AFS scoring system may have prognostic utility
Gomel and Erenus 1990	Determine prognostic value of AFS adhesion scoring system	Pregnancy rates significant greater ($p<0.05$) for group with mild adhesions vs. severe adhesions	Supports the prognostic utility of the AFS scoring system
Mage et al. 1986	Determine prognostic value of an adhesion scoring system using several values for extent and severity of adhesions, very similar to AFS	With increasing adhesion score, intrauterine pregnancy rates and overall pregnancy rates decreased ($p<0.05$)	Supports the prognostic utility of the an adhesion scoring system very similar to that of AFS
Marana et al. 1995	Correlate AFS adhesion scores with ampullary mucosal findings at salpingostomy in pelvic inflammatory disease	AFS scores did not correlate with pregnancy rates	Not supportive of the prognostic utility of the AFS scoring system (see text)
Nagata et al. 1997a	Evaluate whether periovarian adhesions negatively effects IVF results	Several clinical outcomes (pregnancy rates, oocyte recovery, and embryo transfer rates) varied significantly between adhesion groups ($p<0.05$ to $p<0.01$)	Supports the prognostic utility of the AFS scoring system
Nagata et al. 1997b	Determine whether scoring peritubal and periovarian adhesions separately will have prognostic value for infertility	Several clinical outcomes (pregnancy rates, oocyte recovery, fertilization and transfer rates) significantly greater for group with mild adhesions vs. severe adhesions ($p<0.05$ to $p<0.01$)	Supports the prognostic utility of the AFS scoring system
Nagata et al. 1998	Determine whether periovarian adhesions prevent exogenous HCG diffusion into the ovary	Adhesion grade correlates with ability of HCG to diffuse into the ovary ($p<0.01$)	Supports the prognostic utility of the AFS scoring system

4.3 ANALYSIS OF LITERATURE CORRELATING ADHESION GRADE AND CLINICAL OUTCOME

Nagata et al. (1997a) provided clear evidence of a direct correlation between adhesion grade and clinical outcomes. A direct correlation between adhesion scores and pregnancy rate was observed (70%, 67%, 17%, and 10% rate of pregnancy with minimal, mild, moderate and severe adhesions, respectively), as well as a direct correlation between adhesion groups and follicle recovery and embryo transfer at *in vitro* fertilization and embryo transfer (IVF-ET). Nagata et al. (1998) subsequently provided detailed data for individual adhesion scores and outcomes (with linear regression analysis p-values less than 0.01 for several measurements), whereas the other citations correlated clinical outcomes with adhesion classes (absent/minimal, mild, moderate or severe). Mage et al. (1986) also provided clear evidence of a clinical correlation with AFS scores: pregnancy rates in groups with absent, mild, moderate, and severe adhesions were 38.8%, 32.0%, 26.6% and 5.5%, respectively. Therefore, in the literature identified in Table 4.1, investigators demonstrated statistically significant correlations of AFS scores with pregnancy and fertility outcomes.

The remaining four publications correlated clinical outcomes with low-grade (minimal-mild) or high-grade (moderate-severe) adhesions. Gomel and Erenus (1990) reported significantly higher rates of pregnancy for patients with mild adhesions compared to patients with severe adhesions. Nagata et al. (1997b) reported significantly higher rates of pregnancy, oocyte recovery and embryo transfer for patients with mild adhesions compared to patients with severe adhesions. DeBruyne et al (1997) reported a non-significant trend ($p=0.051$) for pregnancy rates in patients with minimal-mild adhesions compared to patients with moderate-severe adhesions. In the single publication that failed to support the prognostic utility of AFS adhesion scoring (Marana et al. 1995), pregnancy outcome was strongly associated with fallopian tube mucosal damage as assessed by salpingoscopy but not with adhesion score. High-grade salpingoscopic lesions were present in over half the patients, irrespective of AFS adhesion score, suggesting that any effects of adnexal adhesions would be obscured by the intra-tubal pathologies. This study was not of sufficient size to evaluate adhesions as an independent variable in groups with equivalent extents of tubal damage.

In addition to the seven publications summarized above in Table 4.1, a substantial number of additional publications provide indirect support for the clinical relevancy of the American Fertility Society Classification of Adnexal Adhesions. Several studies that classify adhesions by criteria similar to that of American Fertility Society (filmy vs. dense, plus an evaluation of extensiveness of adnexal involvement by adhesions) provide statistically significant correlations between adhesion stage and relevant clinical outcomes such as pregnancy rates and treatment of chronic pelvic pain (Caspi et al. 1979, Oelsner et al. 1994, Peters et al. 1992, Pittaway et al. 1985, Raj and Hulka 1982, Stout et al. 1991, Tulandi 1986, Tulandi et al. 1990). In most of these studies, adhesion classification was via a method similar to but simpler than the

AFS method, and the authors did not attempt to evaluate their data with quantitative scores. Although these studies do not utilize the American Fertility Society Classification of Adnexal Adhesions precisely, they each support the concept that clinical outcomes correlate with adhesion stage as assessed by adhesion physical characteristics (severity) and extent, and that moderate or severe adhesions are associated with significantly lower fertility rates or higher rates of pelvic pain.

In contrast to the numerous publications supportive of the American Fertility Society Classification of Adnexal Adhesions and other similar adnexal adhesion classification systems, careful evaluation of the literature identified three articles that failed to support a valid correlation. Marana et al. (1995, included in Table 4.1) and Dubuisson et al. (1994) studied patients with an additional complicating pathology, namely intra-tubal abnormalities. These authors concluded that intra-tubal pathology markedly impacted fertility outcome, and suggested that adhesion classification under these clinical circumstances is not likely to be predictive of outcome in the presence of tubal damage. In a retrospective study, Ozaki et al. (1999) also failed to find a correlation between adhesion score and pregnancy following corrective surgeries for infertility. These authors concluded that their second-look adhesion scoring at 6-9 days after surgery was too early and stated that adhesions do, in fact, relate to pregnancy outcome.

5.0 CONCLUSIONS

Reduction of post-surgical adhesion formation is the largest unmet need in surgical therapeutics facing the pelvic surgeon today. Adhesiolysis is a common treatment in this setting, but subsequent reformation of adhesions is typical, resulting in the public health need for new methods to inhibit adhesion reformation.

Adhesion scoring is typically performed by surgeons to evaluate adjunctive treatments intended to interfere with adhesion formation, and as a prognostic indicator at the time of surgery. The American Fertility Society Classification of Adnexal Adhesions is the most common system utilized in published scientific literature for quantification of adhesions. It is the only system developed and endorsed by a professional society, and has been widely used for over 10 years. As a result, the American Fertility Society Classification of Adnexal Adhesions is the current standard of practice. Evaluation of the literature indicates that this adhesion scoring system provides a valid prognostic marker for relevant clinical outcomes such as pregnancy or chronic pain.

FDA acceptance of adhesion reduction as a valid clinical endpoint in the approval of other products [*e.g.*, INTERCEED, Seprafilm, Biomatrix Hylasine 510(k)] supports the concept that quantitation of site-specific adhesions is a useful, predictive measure of clinical utility. Similarly, data relating the American Fertility Society Classification of Adnexal Adhesions (and related scores) to clinical outcome measures confirm that this methodology is a valid means of demonstrating clinical utility. This is especially evident in fertility studies, where patients with moderate or severe adhesions have a significantly lower pregnancy rate than patients with none, minimal, or mild adhesions. As a result,

patients with moderate or severe adhesion scores, as defined by the American Fertility Society Classification of Adnexal Adhesions, are considered to have failed surgical therapy and are often referred for IVF-ET or other advanced reproductive technologies to achieve pregnancy.

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